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WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/080,767	ERIKSON ET AL.	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-22,24,28-42,45 and 47* is/are rejected.

7)☐ Claim(s) *9,23,25-27,43,44 and 46* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1/15/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

FINAL ACTION

1. Applicant's amendment filed on November 10, 2004 is acknowledged. Claims 1, 6 and 25 have been amended. Claims 1-47 are pending. All of the amendments and arguments have been thoroughly reviewed and considered but they are not found persuasive for the reasons that follow. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims.

This action is made Final.

2. The text of those section of Title 35, U.S.C. Code not included in this action can be found in prior Office action.

Previous Rejections

3. The claim rejection under 35 USC 112 second paragraph directed to claims 1-47 is being withdrawn in view of applicant's arguments. The claim rejection under 35 USC 112 second paragraph directed to claims 7 and 8 is maintained and discussed below. The claim rejection under 35 USC 112 second paragraph directed to claims 10-17 is maintained and discussed below. The prior art rejection under 35 USC 102(b) directed to claims 1-5, 18-22, 24, 28-32, 34, 41, 42, 45, and 47 as being anticipated by Hogan et al. are maintained and discussed. However, the rejections made against claims 25 and 26 as being anticipated by Hogan et al are withdrawn in view of Applicant arguments concerning the close language of the claims. The prior art rejection under 35 USC 102(e) directed to claims 1, 23, 27, 43-44 and 46 as being anticipated by Meyers et al. is withdrawn in view of Applicant's arguments. The prior art rejection under 35 USC 102(e) directed to claims 1, 4, 5, 29-31 and 49 are maintained and discussed below. The

prior art rejection under 35 USC 103(a) directed to claims 32-34, 36-38 and 40 are maintained and discussed below.

Claim Rejections - 35 USC § 112

4. Once again, claims 7, 8 and 10-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

(a) Claims 7 and 8 are indefinite at the recitation of "free nucleobase" because the term has not been clearly defined in the specification and it cannot be determined what constitutes a free nucleobase. For example, does "free nucleobase" means that an extra nucleobase is added to the blocking agent, or does it mean that the nucleobase is different or distinct from the nucleobases of the target and/or probe, or does the term "free nucleobase" means that the base is incapable of base-pairing or hybridizing to the target and/or probe? Additionally, if the "free nucleobase" is to be interpreted as an extra base, how can the free nucleobase be the only nucleobase of the blocking agent? Clarification is required as to what constitutes a "free nucleobase" in the context of the claimed invention.

Applicant's traversal

5. Applicant traverses the rejection on the following grounds: Applicant states that "a free nucleobase" is simply a nucleobase lacking the sugar and phosphate group present in nucleosides and/or nucleotides". Applicant states that the definition is in accordance with conventional meaning in the art. Applicant provides an exhibit of the definition of the term as illustrated in the Medical Dictionary which states that a nucleoside phosphorylase" is an enzyme that catalyzes phosphorolysis of a nucleoside to form the free base and a ribose or deoxyribose as a step in the degradation of nucleic acids and nucleotides.

Examiner's Response

6. Applicant's arguments filed on November 10, 2003 have been fully considered but they are not persuasive for the following reasons: While the examiner acknowledges Applicant definition of the term as illustrated in the Medical Dictionary, the specification does not clarify a meaning of the term and thus the term is still unclear in the context of the claim language. The courts have established that during patent examination, the claims must be interpreted broadly as reasonably allow *(In re Zletz, 893 F.2d321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989).* In this case as stated in the prior office action submitted on March 17, 2003, it cannot be determined in the context of the claim if a "free nucleobase" is in reference to an extra nucleobase added to the blocking agent or a nucleobase that is different or distinct from the nucleobase of the target and/or probe or a base incapable of basepairing or hybridizing to the target and/or probe. Thus the meaning of the term in the context of the claim language is indefinite and the rejection under 35 USC 112 second paragraph is maintained.

(b) Claims 10-17 are confusing at the recitation of "wherein at least one nucleobase is provided in a quantity that is 1-200% of a number of the probe or number of the target nucleobase" because it cannot be determined if reference is being made to a molar concentration or if reference is being made to a length limitation of the nucleobases or if reference is being made to the amount of nucleobases capable of complementarity between the nucleobases of the blocking agent, probe and target. Clarification is required as to what is meant by "a quantity of at least one nucleobase".

Applicant's Traversal

7. Applicant traverses the rejection on the following grounds: Applicant states that the expression "wherein said at least one nucleobase is provided in a quantity that is 1-200% of a

number of said probe nucleobases that are Watson crick complements to said at least one nucleobase" and "wherein said at least one nucleobase is provided in a quantity that is 1-200% of a number of said probe nucleobase that are identical to said at least one nucleobase" would be clear to one of ordinary skill in the art in view of the original disclosure, particularly in the example 1 at page 11, lines 16-19. Applicant states that the calculation for the homologous binding motif is analogous, and also based on molar concentrations.

Examiner's Response

8. Applicant's arguments filed on November 10, 2003 have been fully considered but they are not persuasive for the following reasons: While the examiner acknowledges Applicant's arguments that the specification makes clear the meaning of the term, the courts have established that during patent examination, the claims must be interpreted broadly as reasonably allow *(In re Zletz, 893 F.2d321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989).* In this case as stated in the prior office action submitted on March 17, 2003, the claim as broadly written does not make clear if reference is being made to the amount of nucleobases capable of complementarity between the nucleobases of the blocking agent, probe and target or if is if reference is being made to a length limitation of the nucleobases or if reference is being made to a molar concentration. Thus the meaning of the term in the context of the claim language is indefinite, the specification does not make clear the meaning of the term as written in the claim and therefore the rejection under 35 USC 112 second paragraph is maintained.

Claim Rejections - 35 USC § 102(b)

9. Once again, claims 1-5, 18-22, 24, 28-32, 34, 41, 42, 45 and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Hogan et al. (US 5,030,557, July 9, 1991). Regarding

claim 1, Hogan et al. teach a method of forming a complex between a probe containing probe nucleobases and a target containing target nucleobases, comprising mixing said probe and said target under hybridizing conditions, wherein at least one blocking agent (helper oligonucleotide) comprising at least one nucleobase is conjugated to said target nucleobase prior to hybridizing said probe to said target and wherein said conjugation enhances an avidity and/or specificity of said hybridizing (see abstract and col. 4, lines 19-44 and col. 5, beginning at line 64 to col. 6, line 4). Therefore, the reference of Hogan et al. meets all of the claimed limitations of claim 1.

Regarding claim 2, Hogan et al. teach the method of claim 1, wherein said conjugation enhances said avidity and/or specificity by hindering said probe and/or target from existing in a conformation antithetical to said hybridization (see abstract and col. 4, lines 39-36; see also Figure 3).

Regarding claim 3, Hogan et al. teach the method of claim wherein said conformation is a hairpin structure (see figure 3).

Regarding claims 4 and 5, Hogan et al. teach the method of claim 1, wherein the blocking agent is not greater than about 50 nucleobases, which is interpreted as the blocking agent comprising up to 50 nucleobases (col. 5, lines 64-65).

Regarding claim 18, Hogan et al. teach the method of claim 1, wherein said probe nucleobases are arranged in a probe sequence of interspersed purines and pyrimidines (see col. 8, Ex. 1, lines 20-24, sequences for "Helper A" and "Helper B"). Hogan et al. further teach that the probe may comprise one or more nucleotides not complementary to the corresponding bases in the target sequence (col. 5, lines 49-52; see also col. 6, lines 65-68).

Regarding claims 19 and 20, Hogan et al. teach that the nucleotide (base + sugar + phosphate: col. 5, lines 21-24) probe is an oligonucleotide or polynucleotide and may be an analogue of the phosphate ester structure of a typical DNA or RNA. Hogan et al. states that for

example, the probe may have an alkyl or phosphate, a phosphoraothioate or other modified backbone structure (col. 5, lines 44-55, 59-63). The charge of the nucleotide probe as claimed in claim 20 is inherent in teachings of Hogan et al. of the modified backbone structures which may cause the probe to be uncharged or positively charged.

Regarding claims 21 and 22, Hogan et al. teach the method of claim 1, wherein the target is a property conferred by the base sequence of a single strand of DNA or RNA which, with another DNA or RNA strand, may form a hybrid of double stranded DNA:DNA, RNA:RNA or DNA:RNA (col. 5, lines 32-38).

Regarding claim 24, Hogan et al. teach the method of claim 1, wherein said at least one blocking agent is not conjugated to said probe (see abstract and col. 4, lines 31-33).

Regarding claim 28, Hogan et al. teach the method of claim 1, wherein said probe has a probe directionality anti-parallel to a target strand directionality of said target (col. 6, lines 61-64).

Regarding claim 29, Hogan et al. teach a method of claim 1, wherein the probe is further labeled for detection of the complex (see col. 5, lines 54-59 and Example 1, specifically col. 8, lines 25-63).

Regarding claim 30, Hogan et al. teach the method of claim 29, wherein said complex is capable of being formed when the target DNA is bound to a solid surface (col. 14, 5-8).

Regarding claims 31 and 32, Hogan et al. teach the method of claim 29, wherein said complex is detected by a change in a signal associated with a label wherein the label is a radioisotope (see examples 1 and 2). Hogan et al. further teach wherein the probe can be labeled with any suitable label such as a radioisotope, or an enzyme such as horseradish peroxidase or alkaline phosphatase which catalyzes a color forming reaction of a suitable substrate, or the label may be a fluorometric moiety such as acridinium ester (col. 14, lines 26-34).

Regarding claim 34, Hogan et al. teach the method of claim 29, wherein said detecting is conducted in a tested medium under a varied condition wherein said varied condition is a change in a temperature of a said test medium (col. 14, lines 42-46).

Regarding claim 41, Hogan et al. teach the method of claim 29, wherein a kit is provided for detecting a target nucleic acid. the kit comprises the blocking agent, labeled probe and also includes positive and negative controls and standards for obtaining quantitative results (col. 14, lines 47-54). Therefore, Hogan et al. suggest that the target can be quantitated.

Regarding claim 42, Hogan et al. teach the method of claim 29, wherein an extent of complementarity between the probe and said target is detected (col. 7, lines 19-22).

Regarding claim 45, Hogan et al. teach the method of claim 1, wherein the probe and the target hybridize in accordance with a Watson-Crick motif to form duplex and triplex complexes (see Figures 1-3 and col. 5, lines 32-49, 64-68 and col. 6, lines 1-4).

Regarding claim 47, Hogan et al. teach the method of claim 1, wherein said hybridizing may be conducted in a homogeneous medium (col. 14, lines 18-21). Therefore, Hogan et al. also meet all of the limitations of claims 2-5, 18-22, 24, 28-32, 34, 41, 42, 45 and 47 of the instant invention.

Applicant's Traversal

10. Applicant traverses the rejection on the following grounds: Applicant states that Hogan et al. discloses "helper oligonucleotides" said to bind to target nucleic acid so as to alter a secondary and/or tertiary structure of the target nucleic acid and facilitate binding of the probe to the target. Applicant cites a passage from the patent and states that on the other hand, base claim 1 now specifies that the at least one blocking agent comprising the one nucleobase is conjugated to the probe hybridizing segment and or said target hybridizing segment prior to hybridizing said probe with said target. Applicant states that this is essentially the opposite of binding "the target

nucleic acid without substantially overlapping the region bound by the nucleotide probe. Applicant states that thus, Hogan's teachings of binding a helper oligonucleotide to one portion of a target nucleic acid to enhance biding of a probe to a substantially different portion of the target does not meet all of the features of base claim 1 and dependent claims 4-5, 18-22, 24-26, 28-32, 34, 41, 42, 45, and 47. Applicant further contends that the helper oligonucleotide of Hogan et al. is about 10 to about 50 nucleotides in length wherein claim 4 specifies that the blocking agent contain up to two nucleobases. Applicant states that claim 25 specifies that the at least one blocking agent is a naturally occurring nucleobase selected from the group consisting of A, T, C, G and U. Applicant further contends that the passage of Hogan cited in the support of rejection claim 34 does not teach conducting or detecting under varied conditions. Applicant continues by stating at Hogan at col. 14, lines 42-46 discloses the temperature at which the assay is run. Applicant states that the fact that the temperature (4-5 degrees C varies from room temperature or the Tm of the probe: target hybrid is irrelevant to the claim limitation, which requires varying a condition while conducting the detecting step. Finally, Applicant concludes that the passage of Hogan et al. cited by the Office action in support of rejecting claim 42 does not teach detecting and extent of complementarity between the probe and the target. Applicant suggests that the rejections be withdrawn in light of the arguments.

Examiner's Response

11. Applicant's arguments filed November 10, 2004 have been fully considered but they are not persuasive or the following reasons: The courts have established that during patent examination, the claims must be interpreted broadly as reasonably allow *(In re Zletz, 893 F.2d321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989).* In this case, given the broadest reasonable interpretation of the claim language, the amendment made to the claims does not overcome the prior art rejection because the cited prior art the claimed limitations. While the

examiner agrees that the reference of Hogan et al teaches that the helper oligonucleotide binds to the targeted nucleic acid without substantially overlapping the region bound by a nucleotide probe, the reference is not limited in the way applicant contends. Additionally, Hogan et al. teaches at col. 7, lines 22-24, that "limited overlap between the region recognized by the helper and that recognized by the probe can be tolerated" which means that the helper oligonucleotide is capable of binding to the hybridizing segment of the target nucleic acid as required by the claimed invention. With regards to applicant arguments that the helper oligonucleotide of Hogan is about 10 to about 50 nucleotides in length which differs from that of the claimed invention, it is noted that the term "about 10" provides a overlapping range for the helper oligonucleotide and can be interpreted as from 1 to 10 oligonucleotides in length. MPEP 2131.03 states that prior art which teaches a range within, *overlapping,* or touching the claimed range anticipates if the prior art range discloses the claimed range with "sufficient specificity". Hogan et al meet this requirement in the teachings of the properties of the helper oligonucleotide. With respect to Applicant's arguments concerning claim 34, the examiner respectfully disagree because the reference teaches varying assay conditions for detection. Hogan et al teaches in the Examples wherein the assays were tested in different temperatures from 55 degrees Celsius to 60 degrees Celsius to 37 degrees Celsius (see examples 1-3). Likewise the claims do not define or specify what conditions are varied or how the conditions for the detecting of a complex are varied. The examples provided in the specification do not provide a limiting definition of "varied conditions" for the instant invention. Therefore, given the broadest reasonable interpretation of the claims, Hogan et al. meets this limitation by teaching wherein detection occurs at multiple temperature conditions (varied conditions). With respect to Applicant's arguments against claim 42, the

examiner respectfully disagree. The reference of Hogan provides evidence that the an extent of complementarity between the probe and the target is detected based on the teaching that overlap between the region recognized by the helper oligonucleotide and that recognized by the probe is tolerated.. Applicant's arguments are not sufficient to overcome the prior art rejections recited above. Accordingly, the rejections under 35 USC 102(b) are maintained.

Claim Rejections - 35 USC § 102(e)

12. Once again, claims 1, 4, 5, 29-31, 39 are rejected under 35 U.S.C. 102(e) as being anticipated by Becker et al. (6,130,038, effective filing date, July 1996). Regarding claim 1, Becker et al. teach a method of forming a complex, said method comprising mixing a probe containing probe nucleobase with a target containing target nucleobase under hybridizing conditions, wherein at least one blocking agent (modifying agent) comprising at least one nucleobase is conjugated to said probe and/or said target prior to hybridizing said probe with said target, wherein said conjugation enhances avidity and specificity of said hybridizing (col. 9, lines 42-67 to col. 10, lines 1-25).

Regarding claim 4, Becker et al. teach the method of claim 1, wherein said at least one blocking agent contains up to five nucleobases (col. 8, lines 53-63 and col. 21, lines 42-48).

Regarding claim 5, Becker et al. teach the method of claim 1, wherein said at least one blocking agent contains up to two nucleobases (col. 8, lines 53-59).

Regarding claim 29, Becker et al. teach the method of claim 1, further comprising detecting said complex (col. 11, lines 28-46; col. 12, lines 8-26 and col. 22, lines 46-47).

Regarding claim 30, Becker et al. teach the method of claim 1, wherein said complex is formed with at said target is bound to a substrate (col. 12, lines 12-17).

Regarding claim 31, Becker et al. teach the method of claim 29, wherein said complex is detected by a change in a signal associated with a label (col. 2, lines 44-53)

Regarding claim 39, Becker et al. teach the method of claim 31, wherein said label is added free in solution to said test medium such that it is capable of binding to the desired nucleic acid (col. 3, lines 35-40 and 12, lines 56-67).

Therefore, Becker et al. meets all of the claimed limitations of claims 1, 4, 5, 29-31, 39 of the instant invention.

Applicant's traversal

13. Applicant traverses the rejections on the following grounds: Applicant states that Becker et al. discloses oligonucleotides containing one or more modified nucleotides which increase the binding affinity of the oligonucleotides to target nucleic acids having complementary nucleotide base sequence. Applicant states that Becker discloses that the conjugate molecules attached to oligonucleotides may function to further increase the binding affinity and hybridization rate of these oligonucleotides to target. Applicant contends that Becker disclose that these conjugate oligonucleotides can be referred to as "helper probes" and "helper oligonucleotides". Applicant states that these are the same helper oligonucleotides disclosed by Hogan et al.. Applicant further contends that Becker et al differ from Hogan et al in this regard in that Becker et al teach the use of certain modified nucleotides within the oligonucleotides with or without the helper oligonucleotides. Applicant further argues that the Office Action has further misinterpreted the teaching of Becker et al. with respect to claims 4 and 5. Applicant states that reference to modification of 4 to 5 consecutive nucleotides do not mean that the helper oligonucleotide is 4 or 5 nucleotides in length. Rather, the cited passage refers to nucleotides of the probe having e.g., modified ribofuranosyl rings. Applicant states that Becker et al do not describe how long the helper oligonucleotides can be, although it provides examples of 31 to 41 nucleotides in length and incorporates by reference the teaching of Hogan et al. which defines helper oligonucleotides

as being about 10 nucleotides to about 50 nucleotides in length. Finally Applicant request the rejections be withdrawn.

Examiner's response

14. Applicant's arguments filed November 10, 2003 have been fully considered but they are not persuasive for the reasons cited previously above at No. 11 in response to Applicant's arguments concerning the Hogan et al reference. With respect to Applicant arguments that the Office misinterpreted the teaching of the Becker et al reference in regards to claims 4 and 5, it is noted that while the reference teaches wherein the probe may contain modification of 4 or 5 consecutive nucleotides (single cluster) along with unmodified nucleotides. It is also noted that the reference further teaches wherein the probe may comprise of a 100% modified nucleotide residues (a single cluster) (col. 13, lines 27-31), which may be interpreted as a probe oligonucleotide having 4 or 5 consecutive nucleotides with no unmodified nucleotides. Likewise as indicated above, the cited reference of Hogan et al, as noted by Becker et al, teaches an overlapping range of "about 10 nucleotides to about 50 nucleotides" which encompasses the claimed invention. Therefore, in view of the foregoing the rejection under 35 USC 102(e) is maintained.

35 USC § 103(a)

15. Once again, claims 32-34, 36-38, 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. as previously applied above in view of (Heller et al. 6,048,690, May 1997). Regarding claims 32-33, Hogan et al. teach a method of forming a complex between a probe containing probe nucleobases and a target containing target nucleobases, comprising mixing said probe and said target under hybridizing conditions, wherein at least one blocking agent (helper oligonucleotide) comprising at least one nucleobase is conjugated to said

target nucleobase prior to hybridizing said probe to said target and wherein said conjugation enhances an avidity and/or specificity of said hybridizing.

The method of Hogan et al. differs from that of the claimed invention in that Hogan et al. do not teach wherein in said method the complex is detected by analyzing an electronic characteristic of said complex.

Heller et al. teach a method for hybridization analysis by analyzing an electronic characteristic of the hybridization sample (abstract and col. 1, lines 44-55). Heller et al. teach wherein the method comprises providing a target comprising at least one nucleic acid sequence; providing a probe comprising a nucleic acid sequence; mixing the probe and the target to a hybridization medium to provide a complex, adding to the complex a label wherein said label is an environmental sensitive emission label such as a chromophore or fluorophore or luminescent molecule or moiety or metal chelate or enzyme or peptide or amino acid (col. 6, lines 57059); subjecting the hybridization product and label to a varying elelctrophoretic force, monitoring the emission from the label and analyzing the monitored emission to determine the electronic fluorescent perturbation effect (abstract and col. 5, lines 59-6- 67 to col. 6, lines 1-9) which is a rise or spike in fluorescent intensity prior to dehybridization of a fluorescent labeled probe from a capture sequence attached to a microlocation test tube (col. 4, lines 62-66). Heller et al. further teach that this method is a powerful analytical tool for DNA hybridization analysis, particularly for the near instantaneous, e.g., less than one minute, and especially less than 5 seconds, discrimination of match/mismatched DNA hybrids and is also useful for novel DNA sequencing applications (col. 5, lines 16-21).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the claimed invention to have been motivated to have modified the method of forming a complex as taught by Hogan et al. to encompass detection of the complex by analyzing an electronic characteristic as taught by Heller et al. One of ordinary skill in the art would have been

motivated to do so for the advantages taught by Heller et al. that a method, such as a fluorescent perturbation effect, which utilizes electronic power(current and voltage) as described is a powerful tool for DNA hybridization analysis, particularly for the near instantaneous, e.g., less than one minute, and especially less than 5 seconds, discrimination of match/mismatched DNA hybrids and is also useful for novel DNA sequencing applications.

Regarding claim 34, Heller et al. teach the method of claim 29, wherein the method of detecting is conducted in a test medium under a varied condition, wherein said varied condition is a change in an electric current and change in an electrical property (col. 7, lines 14-16 and col. 10, lines 63-67 to col. 11, line 10, see also Example 3).

Regarding claim 36, Heller et al. teach the method of claim 29, wherein said electrical property is electrical conductance (col. 10, lines 63-65).

Regarding claim 37, Heller et al. teach the method of claim 34, wherein said electrical property is amplitude of a signal propagated in said transmission line in said test medium (col. 9, lines 1-6).

Regarding claim 38, Heller et al. teach the method of claim 34, wherein said complex is detected under serially varied conditions (col. 7, lines 14-16 and col. 10, lines 63-67 to col. 11, line 10, see also Example 3).

Regarding claim 40, Heller et al. teach the method of claim 29, further comprising detecting a signal from a label wherein said signal is correlated to a binding affinity between said probe and said target; varying conditions of a test medium and detecting a subsequent signal and comparing the first signal and subsequent signal (See examples 3 and 4).

Applicant's Traversal

15. Applicant traverses the rejection on the following grounds: Applicant states that Hogan et al. fail to teach the limitations of claim 1 and the secondary reference of Heller et al. does not provide the deficiency not found in Hogan et al. Applicant states that specifically, the reference

of Hogan et al does not disclose that at least one blocking agent comprising at least one nucleobase is conjugated to said probe hybridizing segment and/or said target hybridizing segment prior to hybridizing said probe with said target. Likewise, Applicant argues that regardless of whether Heller et al teaches anything regarding analyzing electronic characteristics of samples, the office actions fails to show how one of ordinary skill in the art would have been motivated with a reasonable expectation of success to modify the teachings of Hogan et al. with the teaching of Heller et al. to reach the claimed invention as amended. Applicant further contends that moreover, measuring an increase in fluorescent intensity (FPE) as the first fluorescent manifestation caused by the electronic denaturation and electrophoresis of DNA hybrids as taught by Heller is not "analyzing an electronic characteristic of said complex as specified in the claims. Applicant states that fluorescent intensity is not an electronic characteristic of a complex as used in claim 33 and respectfully request the rejection be withdrawn.

Examiner's Response

16. Applicant's arguments filed November 10, 2003 have been fully considered but they are not persuasive for the reasons cited previously above at No. 11 in response to Applicant's arguments concerning the Hogan et al reference.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Likewise, as stated in the prior Office Action, Hogan et al. teach a method of forming a complex between a probe and target under hybridization conditions and detecting the complex via the use of a label such as e.g., fluorescent label. Hogan does not teach wherein the complex is detected by analyzing an electronic characteristic of said complex. This limitation is however found in the teaching of

Heller et al. by the use of an electronic stringency control device to analyze the electronic characteristic of a hybridization sample. Heller provides motivation for wanting to utilize a method which measures electronic characteristics of a sample using an electronic device. Heller et al states that such a method which utilizes electronic power (current and voltage) as described is a powerful tool for DNA hybridization analysis, particularly for the near instantaneous, e.g., less than one minute, and especially less than 5 seconds, discrimination of match/mismatched DNA hybrids and is also useful for novel DNA sequencing applications.

With respect to Applicant's arguments that the reference of Heller et al. does not describe measuring an electronic characteristic, it is noted that the specification nor claims does not describe or disclose what an "electronic characteristic" encompass or what is considered an "electronic characteristic" or how the analysis is carried out to determine an electronic characteristic (see spec, paragraph 0024 and claim 33). Therefore, the claim can be interpreted as using an electronic device to which would detect characteristics (e.g., electronic denaturation) of a sample. In view of the foregoing, the rejections under 35 U.S. C. 103(a) are maintained.

17. Claims 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. as previously applied above in view of Wu et al. (5,846,729, filing date July 1, 1997). Regarding claims 35, Hogan et al. teach a method of forming a complex between a probe containing probe nucleobases and a target containing target nucleobases, comprising mixing said probe and said target under hybridizing conditions, wherein at least one blocking agent (helper oligonucleotide) comprising at least one nucleobase is conjugated to said target nucleobase prior to hybridizing said probe to said target and wherein said conjugation enhances an avidity and/or specificity of said hybridizing.

The method of Hogan et al. differs from that of the claimed invention in that Hogan et al. do not teach wherein in said method the complex is detected in a test medium under varied

conditions wherein said varied condition is a change in a number of photons in the test medium. Hogan et al. additionally do not teach wherein a laser beam is applied to said test medium to effect said change in the number of photons.

Wu et al. teach a method of forming a hybridization complex between a target nucleic acid and probe in a test a medium and detecting said hybridization complex by applying a laser beam to the hybridization sample which is capable of effecting changes in the number of photons and measuring signal intensity (col. 3, lines 29-44, col. 5, lines 57-58, col. 6, lines 5-51). Wu et al. teaches that by using this method for detecting hybridization, no separation of the hybridization complex from the uncomplexed probes is necessary prior to signal determination (col. 6, lines 52-54). Wu et al. teach that additionally nucleotide sequence information can be determined by monitoring a change in the overall signal intensity, which is a function of hybridization and hybridization efficiency (col. 6, lines 62-65).

Therefore, in view of the foregoing, it would have been obvious to one of ordinary skill in the art at the time of the claimed invention to have been motivated to have modified the method of detecting a hybridization complex as taught by Hogan et al. to encompass detection of the complex by applying a laser beam capable of effecting changes in the number of photons in a test medium as taught by Wu et al. One of ordinary skill in the art would have been motivated to do so for the advantage taught by Wu et al. that the method, wherein a laser beam is applied to detect a hybridization complex, requires no separation of unhybridized probes from the hybridization complex prior to signal detection and for the advantage that sequence information can be determined by monitoring a change in the overall signal intensity which is a function of hybridization and hybridization efficiency.

Applicant's Traversal

18. Applicant traverses the rejection on the following grounds: Applicant states that Hogan et al. fail to teach the limitations of claim 1 and the secondary reference of Wu et al. does not

provide the deficiency not found in Hogan et al. Applicant states that specifically, the reference of Hogan et al does not disclose that at least one blocking agent comprising at least one nucleobase is conjugated to said probe hybridizing segment and/or said target hybridizing segment prior to hybridizing said probe with said target. Likewise, Applicant argues that regardless of whether Wu et al teaches anything regarding altering photonic conditions of samples, the office actions fails to show how one of ordinary skill in the art would have been motivated with a reasonable expectation of success to modify the teachings of Hogan et al. with the teaching of Wu et al. to reach the claimed invention as amended. Applicant respectfully request the rejection be withdrawn.

Examiner's Response

19. Applicant's arguments filed November 10, 2003 have been fully considered but they are not persuasive for the reasons cited previously above at No. 11 in response to Applicant's arguments concerning the Hogan et al reference. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Likewise, as stated in the prior Office Action, Hogan et al. teach a method of forming a complex between a probe and target under hybridization conditions and detecting the complex via the use of a label such as e.g., a fluorescent label. Hogan et al do not teach detecting the complex under varied conditions wherein said varied condition is change in photons. Nor does the reference teach wherein a laser bean is applied to the test medium to effect the change in the number of photons. These limitations however are found in the reference of Wu et al. As stated in the prior Office action, Wu teaches a method of forming a hybridization complex between a target nucleic acid probe in a test medium and detecting said hybridization complex by applying a laser bean to the hybridization sample which is capable of effecting changes in the number of

photons and measuring the signal intensity. W provides motivation for doing so in the teaching that applying a laser bean to detect a hybridization complex is advantageous because it requires no separation of unhybridized probes from the hybridization complex prior to signal detection. Therefore, in view of the foregoing the rejection under 35 USC(a) is maintained.

New Grounds of Rejections

THE NEW GROUND(S) OF REJECTION WERE NECESSITATED BY APPLICANT'S AMENDMENT OF THE CLAIMS:

New Matter Rejection

Claim Rejections - 35 USC § 112

20. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

21. Claims 1 and 6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claimed invention is drawn to a method of forming a complex between a probe containing probe nucleobase and a target containing target nucleobase, comprising mixing said probe and said target under hybridizing conditions such that a probe hybridizing segment of said probe hybridizes to a target hybridizing segment of said target, the improvement wherein at least one blocking agent comprising at least one nucleobase is conjugated to said probe hybridizing segment and/or said target hybridizing segment prior to hybridizing said probe with said target, wherein said conjugation enhances an avidity and/or specificity of said hybridizing. The claim 6

is identical to claim 1 but further encompass "wherein said at least one nucleobase is the only nucleobase contained in said at least one blocking agent, and said conjugation enhances acidity and/or a specificity of said hybridizing. Nowhere in the specification is there a disclosure wherein a probe hybridizing segment of said probe is hybridized to a target hybridizing segment of a target. Nowhere in the specification is there a disclosure wherein "a blocking agent comprising at least one nucleobase is conjugated to a probe hybridizing segment and/or a target hybridizing segment prior to hybridizing said probe with said target". Applicant provides no cited support for the new limitations of claims 1 and 6 and thus a review of the specification does not depict what is claimed. The specification throughout teaches that the invention provides an improved method of forming a complex between a probe containing a probe nucleobase and a target containing a target nucleobase, comprising mixing the probe and the target under hybridizing conditions, wherein at least one blocking agent comprising at least one nucleobase is conjugated to said probe and/or target prior to hybridizing said probe with said target". The example beginning at paragraph 0039 do not describe "wherein a blocking agent comprising at least one nucleobase is conjugated to the probe hybridizing segment and/or target hybridizing segment prior to hybridizing the probe with the target". Likewise, the drawings do no indicate where the blocking agent is conjugated. In fact, there is no disclosure anywhere in the specification which teaches where the blocking agent is conjugated in relations to the probe and/or target. The specification and example merely discloses that hybridization of the probe and target occurs in the presence of a blocking agent (see example 1). Therefore, the specification would not have suggested to the skilled artisan that the applicant was in possession of the claimed invention as of the filing date of the application.

Conclusion

22. Claims 1-8, 10-22, 24, 28-42, 45 and 47 are rejected. Claims 9, 23, 25-27, 43, 44 and 46 are objected to as depending from rejected claims. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (703) 305-1680. After January 14, 2004, the examiner cam be reached at (571) 272-0791. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be emailed to cynthia.wilder@uspto.gov. Since email communications may not be secure, it is suggested that information in such request be limited to name, phone number, and the best time to return the call

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308 0196.

cw
1/22/04

BJ FORMAN, PH.D.
PRIMARY EXAMINER